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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/834,321	04/13/2001	Jeffrey V. Ravetch	TRU-0005	2584

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EXAMINER	
BELYAVSKYI, MICHAIL A	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 06/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/834,321	RAVETCH, JEFFREY V.	
	Examiner	Art Unit	
	Michail A. Belyavskyi	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 April 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,10-13,15 and 23-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,10-13,15 and 23-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 04/06/06 is acknowledged.

2. Claims 1,10-13, 15 and 23-38 are pending and under consideration in the instant application.

3. Applicant's submission of International Search Reports on the IDS, filed 10/14/04 has been considered, however said citation has been crossed out as it is not appropriate for printing in an issued patent.

In view of the amendment, filed 04/06/06, the following rejections remain:

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1, 10-13 and 23-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention for the same reasons set forth in the previous Office Action, mailed 01/28/04.

Applicant's arguments, filed 04/06/06 have been fully considered, but have not been found convincing.

Applicant asserts that: Claim 1 has been amended to recite that the therapeutic antibody whose cytotoxicity is enhanced by the present invention retains or has enhanced binding to activating Fc receptors and that the Fc region of the antibody is at least 80 % homologous with a native Fc region. As amended, the claims variously recite limitations on the structural changes made to the therapeutic antibody and specific functions which the final product possesses.

It is noted that amendments to claims 1, 10-13 and newly cited 23-38 have added the function of the therapeutic antibody. However, these amendments do not obviate the issues of enablement rejection set forth in the previous office action of 01/28/04. Applicant is relying upon certain biological activities but provided no sufficient guidance to support an entire genus. The claims as written encompass a broad genus of therapeutic antibody with an unlimited number of

possibilities with regard to the modified Fc region sequence. Further, the enablement issues of making said antibodies still remain because the specification does not teach how to make an antibody that have a reduced binding affinity for FcRIIB , due to modification of the Fc portion of the antibody , while retaining or enhancing binding to FcRIIA and Fc RIIIA and use them in a method for enhancing cytotoxicity elicited by antibody *in vivo,* which method comprises disrupting activation of SH2 domain containing inositol 5-phosphatase (SHIP) by FcRIIB . Therefore, absent the ability to predict which of these antibodies would function as claimed, and given the lack of data on regions critical for activity, for one of skill in the art to practice the invention as claimed would require a level of experimentation that is excessive and undue.

A description of a protein by functional language in the absence of a structure is not considered sufficient to show possession of the claimed invention. See Fiers, 984 F.2d at 1169-71, 25 USPQ2D at 1605-06. It is only a definition of a useful result rather than a definition of what achieves that result. Many species may achieve that result. The definition requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736 /f.2d 1516, 1521, 22 USPQ 369, 372-73 (Fed. Cir. 1984) affirming the rejection because the specification does "little more than outline[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.") Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what the material consists of (e.g. structural feature), is not a description of that material.

Since the instant fact pattern fails to indicate that representative number of structurally related compounds, i.e. the genus of antibodies that have a reduced binding affinity for FcRIIB , due to modification of the Fc portion of the antibody , while retaining or enhancing binding to FcRIIA and Fc RIIIA the artisan would not know the identity of a reasonable number of representative compounds falling within the scope of the instant claims and consequently would not know how to make them. An assay for *finding* a product is not equivalent to a positive recitation of *how to make* a product.

Moreover, it is noted that in Example 1, FcγRIIB deficient mice, i.e. mice lacking FcγRIIB was used. The amended claim 1 recited a method for enhancing cytotoxicity by therapeutic antibody, which method comprises disrupting activation of SHIP by FcγRIIB caused by binding of the antibody to said receptor. It is not clear how the example using the mice lacking said receptor support the operability of the method that required the presence and activity of said receptor? Moreover, Pearse et al., (Pearse et al., Immunol., 1999, Vol.10, pages 753-760) teach that interpretation of data obtained on mice deficient in FcγRIIB is complicated, since animals deficient in the inhibitory receptors have different responses compare to control ones (see entire document, page 756 in particular).

It is the examiner position that the specification does not provide sufficient guidance and examples as to which modifications would be acceptable to retain these specific structural and functional properties of claimed antibodies to be used in the claimed method for enhancing cytotoxicity elicited by antibody *in vivo,* which method comprises disrupting activation of SHIP

by FcRIIB. In addition, the term "modifying" encompass any substitution, deletion or insertion (page 14, lines 13-16 of Specification as filed) of Fc portion of the antibody that will affect their structural and functional properties. Applicant acknowledges that single amino acid replacement in Fc portion of the mouse anti-HER2 antibody 4D5 reduces affinity for **both** FcRII and FcRIII receptors (page 35, lines 5-20 of the Specification as filed). The references cited by the examiner indicated that protein chemistry is probably one of the most unpredictable areas of biotechnology and that it is known in the art that even single amino acid changes or differences in a proteins amino acid sequence can have dramatic effects on the protein's function.

Thus, Applicant has not provided sufficient guidance to enable one skill in the art to use claimed method for enhancing cytotoxicity elicited by a therapeutic antibody *in vivo*, which method comprises disrupting activation of SHIP by Fc RIIB in manner reasonably correlated with the scope of the claims. *In re Fisher*, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In view of the quantity of experimentation necessary, the unpredictability of the art, the lack of sufficient guidance in the specification, lack of working examples, and the limited amount of direction provided given the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

6. Claims 1, 10-13 and 23-38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the same reasons set forth in the previous Office Action, mailed 01/28/04

Applicant's arguments, filed 04/06/06 have been fully considered, but have not been found convincing.

Applicant asserts that Claim 1 has been amended to recite that the therapeutic antibody whose cytotoxicity is enhanced by the present invention retains or has enhanced binding to activating Fc receptors and that the Fc region of the antibody is at least 80 % homologous with a native Fc region. As amended, the claims complies with written description requirenment.

Contrary to applicant assertion, it is the examiner position that the claims as written encompass the genus of antibodies that have a reduced binding affinity for FcRIIB , due to modification of the Fc portion of the antibody , while retaining or enhancing binding to FcRIIA and Fc RIIIA that can be used in a method for enhancing cytotoxicity elicited by a this antibody *in vivo*, which method comprises disrupting activation of SHIP by Fc RIIB .

There does not appear to be an adequate written description in the specification as-filed how to make an antibody that have a reduced binding affinity for FcRIIB , due to modification of the Fc portion of the antibody , while retaining or enhancing binding to FcRIIA and Fc RIIIA and use them in a method for enhancing cytotoxicity elicited by antibody *in vivo,* which method comprises disrupting activation of SH2 domain containing inositol 5-phosphatase (SHIP) by FcRIIB .

A description of what a material does rather than of what it is, usually does not suffice. The patent does not more than describe the desired function of the compound called for and contains no information by which a person of ordinary skill in the art would understand that the inventors possessed the claimed invention. At best, it simply indicates that one should run tests on a wide spectrum of compounds in the hope that at least one of them will work. Inadequate written description that merely identifies a plan to accomplish an intended result "is an attempt to preempt the future before it has arrived" *Fiers v. Revel*, 984 F.2d 1164,1171 9Fed.Cir. 1993).

The Examiner notes that the claimed invention which is drawn to a genus of antibodies may be adequately described if there is a (1) sufficient description of a representative number of species, or (2) by disclosure of relevant, identifying characteristics sufficient to describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize applicant was in possession of the claimed invention. To satisfy the disclosure of a "representative number of species" will depend on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. "Relevant, identifying characteristics" include structure or other physical and /or chemical properties, functional characteristics coupled with a known or disclosed correlation between function and structure, or a combination of such identifying characteristics sufficient to show the applicant was in possession of the claimed genus. (see Revised Guidelines for the Examination of Patent Applications Under the 35 U.S.C.112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No.4, pages 1099-1111, Friday January 5, 2001).

In the instant case, however, there is no described or art-recognized correlation or relationship between the structure of the invention, modified antibody, that reduced binding affinity for FcRIIB , due to modification of the Fc portion of the antibody , while retaining or enhancing binding to FcRIIA and Fc RIIIA that can be used in a method for enhancing cytotoxicity elicited by a this antibody *in vivo*, which method comprises disrupting activation of SHIP by Fc RIIB, the feature deemed essential to the instant invention. Therefore, one of skill in the art would not envisage, based on the instant disclosure, the claimed method for enhancing cytotoxicity with an antibody, wherein the antibody are specific for a HER2/neu growth factor receptor or for CD20 B cell antigen.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons

of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Revised Guidelines for the Examination of Patent Applications Under the 35 U.S.C.112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No.4, pages 1099-1111, Friday January 5, 2001).

The following new ground of rejection is necessitated by the amendment filed 04/06/06

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8 . Claims 1, 10-13 and 23-38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a New Matter rejection**.

"while retaining or enhancing binding to activating Fc receptors" claimed in 1 represent a departure from the specification and the claims as originally filed. The passages pointed by the applicant do not provide a clear support for the general term "activating Fc receptors". The specification and the claims as originally field only support " while retaining or enhancing binding to FcRIIA and FcRIIIA receptor".

9. No claim is allowed

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

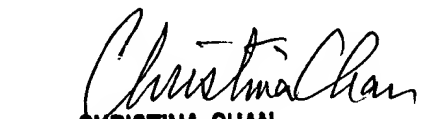
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is 571/ 272-0840 The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571/ 272-0841 .

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Michail Belyavskyi, Ph.D.
Patent Examiner
Technology Center 1600
May 30, 2006



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